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Exploring pH Dependent Landscape Shifts of Proteins

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Molecular dynamics(MD) simulations of proteins at physiological versus lower pH lead to separate stable conformations that do not interconvert. Although modulating pH requires adjusting the ionization states of many residues, we find this effect is achievable by introducing external force on a single one[1]. This finding has far reaching implications for controlling protein conformational dynamics.

We thus perform all-atom MD simulations of 200ns under a series of pH and ionic strength conditions to determine the conformational distributions of calmodulin and ferric-binding protein. For example, in accord with FRET experiments, in calmodulin we find that pH of 5.0 encourages a more compact conformation where the two lobes directly interact, while at 7.4 the lobes are distal, communicating through the linker region[3]. Time scale of the conformational change between the two states is measured on milliseconds[3], way beyond what is observable through MD.

At a coarse-grained level where each residue is treated as a single node, we scan the protein to determine forces that may be inserted on specific residues to cause the observed conformational change. This method, which operates in the linear response regime, points to a single charged residue with upshifted pKa in both proteins[1,4], although the latter information is not encoded in the model.

We implement these findings into steered-MD, where the determined external force acts on the resolved residue, and the protein readily lends itself to the more compact form. Thus, the coarse-grained approach is not only an efficient method determining the main residue whose interactions lead to conformational arrest, but also suggests alternative scenarios to overcome factors hindering barrier crossing.

[1] Atilgan et al. J Chem Phys, in press (2011).
[2] Atilgan et al. Ann Rev Biophys, to appear (2012).
[3] Slaughter et al. Biochemistry (2005).
[4] Atilgan et al. PLoS Comput Biol (2009).

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Transition Pathways of Proteins Explored by Combining Molecular Dynamics Simulations and Monte Carlo Sampling of Collective Modes

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The conformational transition of proteins is explored using a molecular dynamics (MD) simulation protocol which is guided by the normal modes derived from coarse-grained anisotropic network model (ANM). The methodology applies to the cases where the passage from one substate to another (e.g., the open and closed forms of an enzyme, or outward-facing and inward-facing states of a transporter) within a global energy minimum (native state) involves relatively low energy barriers, based on the assumption that low energy barriers may be surmounted/overlooked by adopting a coarse-grained description of the structure and energetics, which smoothes out the energy landscape. The basic approach is to deform the structure along ANM modes, similar to the adaptive ANM (*a*ANM) procedure adopted in our previous work,(Yang et al., 2009) but with the major improvement that the intermediate structures are selected from the complete pool of all accessible ANM modes of motion using a Monte Carlo/Metrolopis algorithm. Application to two proteins with different functional mechanisms, *Escherichia coli* adenylate kinase (AK) and dopamine transporter, shows that the transition between the two alternative forms does not necessarily obey the same pathway(s). For example, in the case of AK, the open-to-closed (O->C) and closed-to-open (C->O) transitions of AK proceed via distinct intermediate conformers: the ATP-binding (LID) domain closing (opening) takes place faster than the nucleotide monophosphate-binding (NMP) domain closing (opening) in the O->C (C->O) transition.

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A Phylogenetic Analysis of Normal Modes Evolution in Enzymes and its Relationship to Enzyme Function

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Enzyme function and catalysis is often dictated by the vibrational dynamics and flexibility of the protein. Since the catalytic functions of enzymes are necessary in nearly all biochemical pathways essential for life, evolutionary conservation of the dynamics that aid enzymatic function is an expected outcome. In this study, a novel phylogenetic approach is implemented to explore the relationship between enzyme dynamics and function as it relates to evolutionary history. Protein dynamics and flexibility are described by normal mode analysis based on a simplified harmonic potential force field applied to the Cα backbone while enzymatic function is described by the Enzyme Commission (EC) numbers in the ENZYME database. Analyzing the comparative normal mode analysis of a catalytic domain family with respects to its phylogenetic tree revealed a negative correlation in dynamic conservation as evolutionary distance increases, which has not been accounted for in prior studies. By correcting the overlap scores of the normal modes for the natural negative relationship, a new score dependent on evolution can be obtained. This novel approach exhibited potential for predicting functional divergence in a protein family's phylogeny and adds a new layer of insight in regards to the role of protein dynamics in enzyme evolution.

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Linkage Between Dynamics and Assembly of Ribosomal Proteins

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Assembly of the ribosome from its protein and RNA constituents has been studied extensively over the past 50 years, and experimental evidence suggests that prokaryotic ribosomal proteins undergo conformational changes during assembly. However, to date, no studies have attempted to elucidate these conformational changes. The present work utilizes computational methods to analyze protein dynamics and to investigate the linkage between dynamics and binding of these proteins played during the assembly of the ribosome. We studied the dynamics of three primary proteins from *E. coli* and *T. thermophilus* 30S subunits (S15, S17, and S20) with atomic molecular dynamic simulations, followed by a study of all r-proteins using elastic network models. We find that r-proteins contain a higher than average percentage of positive residues (Lys + Arg is 18.7% for *E. coli* and 21.2% for *T. thermophilus*). Also, positive residues constitute a large proportion of RNA contacting residues (39% for *E. coli* and 46% for *T. thermophilus*). This indicates the importance of charge-charge interactions in the assembly of the ribosome. Molecular Dynamics simulations show that solvent-exposed proteins (S15 and S17) tend to adopt more stable solution conformations than an RNA-embedded protein (S20). We also find protein residues that contact the 16S rRNA are generally more mobile in comparison with the other residues. This is because there is a larger proportion of contacting residues located in flexible loop regions. Using elastic network models, which are computationally more efficient, we show that this trend holds for most of the 30S r-proteins.

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Coarse-Grained Simulations on Multimeric Assembly of Ligand-Binding Domains in Nuclear Receptors

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We present a coarse-grained model to simulate the assembled conformational shapes of ligand-binding domains (LBDs) in several nuclear receptors. This Coarse-Grained model for protein Assembly (or CGA) includes intra- and inter-domain interactions. In the CGA model, each domain is modeled after its known structure, while for inter-domain interactions, physical and statistical potentials are optimized and balanced in order to achieve realistic pair-wise distance distributions between residues on domain surfaces that interact. The model is first parameterized and validated for three distinct LBD systems with low sequence identity, and then applied to the two members of the nuclear receptor superfamily: retinoid X receptor (RXR) and estrogen receptor (ER). With the help of enhanced sampling strategies, a total of 1000-nsec CGA simulations are obtained for each in order to navigate the physically-accessible configurational space. Finally, a two-step clustering analysis is performed to determine the set of available assembled conformations. The development and application to investigating RXR and ER assemblies using CGA simulations allow us to explore their protein-protein assembly landscape linking to their critical cellular functions.

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Using Delaunay Tessellation of Proteins to Improve Current ENM

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Elastic Network Models (ENM) have long been used as a fast method to extract information about protein dynamics and flexibility. Given the simplicity of ENMs_they are based only on the network of interactions described by the